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(19)

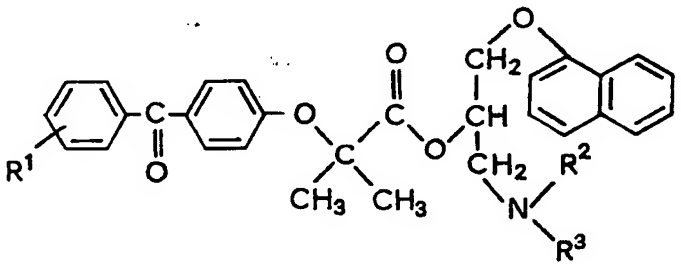
(54) SUBSTITUTED ESTERS OF PHENOXYISOBUTYRIC ACIDS

(71) We, LABORATOIRES BIOSEDRA, a French Body Corporate of 42 Avenue Augustin Dumont, 92, Malakoff, France, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with new propyl esters of phenoxyisobutyric acids, the preparation thereof and pharmaceutical compositions containing them.

It has now been found, in accordance with the present invention, that certain propyl esters of phenoxyisobutyric acid, as hereinafter defined, possess interesting pharmacological activity, especially as hypolipemic agents and β-blocking agents.

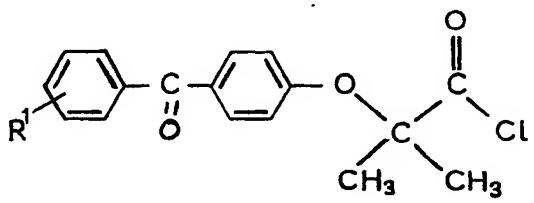
According to the invention, therefore, there are provided as new compounds, compounds of the formula:



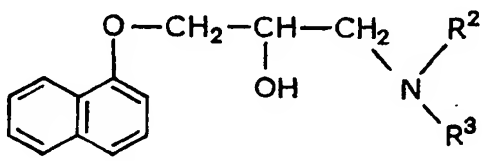
in which R^1 is a hydrogen or halogen atom, especially a chlorine atom in the 4-position in the phenyl rings; and

R^2 and R^3 are the same or are different and each is a hydrogen atom or an alkyl group.

The compounds of the invention may be prepared by the reaction of an appropriate phenoxyisobutyric acid chloride of the formula:



(in which R^1 has the meaning defined above)
with an appropriate aryloxy propanolamine of the formula:



(in which R^2 and R^3 have the meanings defined above).

The phenoxyisobutyric acids used in this process may be synthesized by conventional methods (for example by the Bargellini reaction).

The following Table 1 lists, by way of example, three compounds of the invention which have been prepared.

TABLE 1

Code No.	Compound No.	R^1	R^2	R^3	(°C) m.p.
B2600	I	Cl	C_2H_5	C_2H_5	110–112°
B2601	II	Cl	H	$-CH(CH_3)_2$	89–92°
B2602	III	Cl	H	$-CH(CH_3)-CH_2-CH_3$	72–75°

The following Example illustrates the preparation of compound No. II.

Example.

1-(α-naphthoxy)-3-isopropylamino-prop-2-yl. 4-(4'-chlorobenzoyl-phenoxy)-isobutyrate.

A mixture of 34 grams of 4 - (4' - chlorobenzoyl) - phenoxy isobutyl chloride and 20 grams of 1 - (α - naphthoxy) - 3 - isopropylaminopropan - 2 - ol is heated with stirring for 18 hours at 140° C.

The reaction mixture is cooled and then stirred with an aqueous solution of sodium bicarbonate. The reaction mixture is then extracted with ether and the ether distilled off from the extract to give 31 grams of the final product, compound No. II, m.p. 89—92° (ethanol).

As indicated above, the compounds of the invention possess useful properties as hypolipemic and β-blocking medicaments. These properties are demonstrated below for compounds Nos. I and II as compounds with known medicaments having properties in these fields.

In the first place, the hypolipemic activity of compounds Nos. I and II was compared with that of clofibrate in a five day trial in the rat (Charles River). To this end the compounds under test were mixed with the feedstuff for the rats in an amount of 0.25% in the case of clofibrate and in an amount of only 0.05% for the two compounds according to the invention. The results, expressed as the percentage reduction in total lipids, total cholesterol and triglycerides in the blood are shown in Table II below.

TABLE II

Compound	Total lipids	Total Cholesterol	Triglycerides
Clofibrate	−35	−30	−45
B2600 (Compound No. I)	−21	−25	−46
B2601 (Compound No. II)	−22	−27	−54

As may be seen from the table, the compounds according to the invention are almost as effective as clofibrate at doses which are five times weaker.

In the second place, comparative trials were carried out to compare the β-blocking action of compound No. II with propanolol. As a result it was found that the ED_{50} for beta-blocking activity, namely the inhibition of Tachycardia provoked in the dog by isoproerenol was 0.225 mg/Kg for propranolol whilst a dose of 10 mg/Kg was required for compound No. II to obtain the same result 60 minutes after oral administration.

As a result of these trials it may be seen that compound No. II has the following combination of properties:—

(1) it is hypolipemic agent at least 4 times as active as clofibrate;

(2) it is a beta-blocking agent 30 times as weak as propranolol.

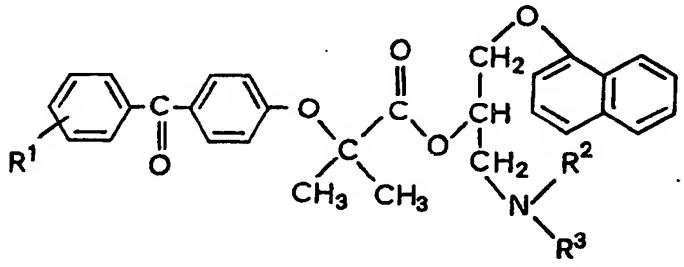
It is therefore possible to use this medicament in hypocholesteremic and hypotriglyceridemic doses without the risk of being troubled by beta-blocking action since the relationship between the two activities makes it possible to employ doses leading to an effective reduction in lipids whilst at the same time leading to a very limited reduction in heart work, as a result of which the prophylactic and therapeutic advantages are remarkably advantageous.

The compounds of the invention are, therefore, very useful in human therapy, in the treatment of hypercholesterolemia and hypertriglycidemia in adults, especially in arteriosclerotics having accelerated heart rates, hypertensives, patients suffering from coronary insufficiency, patients suffering from fibrillation or auricular flutter, or patients having an extrasystolic arythmia.

The invention also provides a pharmaceutical composition comprising a compound in accordance with the invention in association with a pharmaceutical carrier or diluent. In particular the compounds of the invention may be presented in orally administrable forms (such as capsules, tablets or dragees) and administered at dosages of from 0.5 to 1.5 gm/day.

WHAT WE CLAIM IS:—

1. As new compounds, compounds of the formula:



in which

R^1 represents a hydrogen or halogen atom; and

R^2 and R^3 are the same or are different and each is a hydrogen atom or an alkyl group.

2. Compounds as claimed in claim 1 in which R^1 represents a chlorine atom in the 4-position in the phenyl ring.

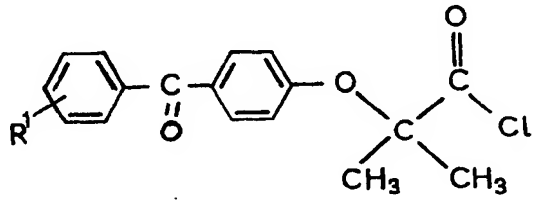
3. 1 - (α - naphthoxy) - 3 - diethylamino - prop - 2 - yl
4 - (4′ - chlorobenzoyl) - phenoxyisobutyrate.

4. 1 - (α - naphthoxy) - 3 - isopropylamino - prop - 2 - yl
4 - (4 - chlorobenzoyl) - phenoxyisobutyrate.

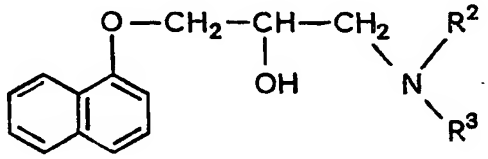
5. 1 - (α - naphthoxy) - 3(2 - butylamino) - prop - 2 - yl
4′ - (4′ - chlorobenzoyl) - phenoxyisobutyrate.

6. A pharmaceutical composition comprising a compound as claimed in any one of claims 1—5 in association with a pharmaceutical carrier or diluent.

7. A process for the preparation of a compound as claimed in claim 1 which comprises reacting a compound of the formula:—



(in which R′ has the meaning defined in claim 1) with a compound of the formula:



in which R^2 and R^3 have the meanings defined in claim 1).

8. A process as claimed in claim 7 substantially as hereinbefore described with reference to the Example.

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